REMARKS

Claims 25-31 are pending and there remain two outstanding issues. One is whether the Office may require restriction between nucleic acid sequences within a single claim. It is respectfully submitted that the Office may not properly restrict between the three nucleic acid sequences specified in each independent claim. The second is whether the claims have utility and whether the specification enables their use in accordance with 35 U.S.C. § 101 and 112, first paragraph. It is respectfully submitted that the claimed methods have well-established, specific, substantial and credible utilities and the specification teaches such uses.

Response to Restriction Requirements

In the Office action response filed January 31, 2003, the applicants elected the species of SEQ ID NO: 23 with traverse in response to the species election requirement set forth in paper no. 24 mailed December 31, 2002. In the Office action mailed May 6, 2003, the Office stated that the species election requirement was meant to be constructed as a restriction requirement and made the requirement final. The Office deemed for the first time in the Office action mailed May 6, 2003 that the election of SEQ ID NO: 23 was a requirement for restriction. Therefore, it is respectfully submitted that making the restriction requirement final was improper. Accordingly, it is respectfully requested that the Office withdraw the finality of the restriction requirement in the Office action mailed May 6, 2003 and consider the following remarks.

The claims are directed in part to processes for screening T-type calcium channel agonists and antagonists, where the channel is encoded by a nucleotide sequence which hybridizes to a nucleic acid comprising SEQ ID NO: 23, 25 or 27. It has long been held that the Office may not impose a restriction requirement on a single claim. *See In re Watkinson*, 14 USPQ.2d 1407 (Fed. Cir. 1990) citing *In re Weber*, 198 USPQ 328, 332 (CCPA 1978) and *In re Haas*, 198 USPQ 334, 336 (CCPA 1978). The courts have definitively ruled that the statute authorizing restriction practice (*i.e.* 35 U.S.C. § 121) provides no authority to impose a restriction requirement on a single claim, even if the claim presents multiple independently

patentable inventions. In these cases, the courts expressly ruled that there is no statutory basis for rejecting a claim for misjoinder, despite previous attempts by the Office to fashion such a rejection. As noted in *In re Weber*:

> The discretionary power to limit one applicant to one invention is no excuse at all for refusing to examine a broad generic claim, no matter how broad, which means no matter how many independently patentable inventions may fall within it.

In re Weber at 334.

Alleging that a particular claim represents multiple "patentably distinct" inventions is a *de facto* rejection of the patentability of the claim because the claim cannot issue as drafted. In this regard the courts noted:

> As a general proposition, an applicant has a right to have each claim examined on the merits. If an applicant submits a number of claims, it may well be that pursuant to a proper restriction requirement, those claims will be dispersed to a number of applications. Such action would not effect the rights of the applicant eventually to have each of the claims examined in the form he considers to best define his invention. If, however, a single claim is required to be divided up and presented in several applications, that claim will never be considered on the merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the subgenera would be defined by the examiner, rather than by the applicant, it is not inconceivable that a number of fragments would not be described in the specification.

See In re Weber , *supra,* emphasis added.

Instead of improperly imposing a restriction requirement on a given claim, the Office may limit initial examination to a "reasonable number" of species encompassed by the claim (*see* 37 C.F.R. § 1.146). This practice strikes an appropriate balance between administrative concerns of the Office and the clear constitutional and statutory rights of the inventor to claim an invention as it is contemplated. *See* MPEP at § 803.02; *In re Wolfrum*, 179 USPQ 620 (CCPA 1973); and *In re Kuehl*, 177 USPQ 250 (CCPA 1973). Unlike a restriction requirement, a species election does not preclude an applicant from pursuing the original form of a claim in subsequent

prosecution nor does it force an applicant to file multiple divisional applications that are incapable of capturing the intended scope of the application. Here, it should be clear that the added cost of filing and prosecuting multiple patent applications does not strike an appropriate balance between the administrative concerns of the Office and the applicants' statutory rights as inventors.

It also respectfully is submitted that there is no undue search burden on the Office when performing a database search for the pending claims. A search that covers one of the specified nucleic acid sequences should be broad enough to cover the two other related nucleic acid sequences. As one search should cover all three nucleotide sequences claimed, there should be no undue search burden on the Office. Accordingly, the applicants again provisionally elect claims directed to the use of the α_1 subunit species encoded by a nucleotide sequence that hybridizes to a nucleic acid comprising SEQ ID NO: 23, and request, respectfully, reconsideration of the restriction requirement.

The Claimed Subject Matter has a Well-Established Utility

The Office rejected the pending claims as the specification allegedly does not provide a specific, substantial or credible utility for the claimed subject matter. These rejections under 35 U.S.C. §§ 101 and 112, first paragraph respectfully are traversed. There are at least six features underscoring the utility of the claimed screening assays:

1. the α_1 subunits encoded by nucleotide sequences that hybridize to a nucleic acid comprising SEQ ID NO: 23, 25 or 27 are functional full-length subunits and the specification teaches a person of ordinary skill in the art how to use the specified α_1 subunits screening assays;

2. publications at the time the priority application was filed demonstrate T-type calcium channel assays had a well-established utility as they were useful for identifying compounds that treat diseases such as hypertension, stroke, epilepsy, heart disease and cancer;

3. a declaration submitted by Dr. Snutch, which must be considered by the Office, demonstrates the claimed screening methods are useful for identifying molecules that treat T-type calcium channel related diseases;

4. due to the facts delineated in items 1, 2 and 3, the screening assays have a well-established, specific, substantial and credible utility for identifying compounds useful for treating diseases enumerated in the specification;

5. little or no experimentation is required beyond the claimed processes to identify compounds that treat diseases listed in the specification; and

6. the Office already has allowed claims directed to T-type channels, proving that claims directed to their use have utility.

The following describes these features in greater detail.

First, the α_1 subunits encoded by nucleotide sequences that hybridize to a nucleic acid comprising SEQ ID NOs: 23, 25 or 27 form functional full-length calcium channels (*see e.g.*, specification on page 5, line 1, and page 24, lines 10-18). Although the properties of these channels may be modulated by co-expression of other subunits, the α_1 subunits alone are functional. The specification also clearly states on page 7 that the subunits are by themselves T-type calcium channels and teaches the person of ordinary skill in the art how to make recombinant cells utilized in the claimed methods (*see e.g.,* page 16, lines 19-27). The specification also teaches methods of using such receptors and recombinant cells in standard methods for screening agonists and antagonists. These well-established methods include whole patch clamp analysis, single channel analysis, ^{45}Ca uptake, fluorescence spectroscopy using calcium sensitive dyes such as FURA-2, and binding or displacement of radiolabeled ligands that interact with the calcium channel (*see e.g.,* page 22, lines 4-9). The Office recognized that the specification teaches these uses of the claimed processes as it admitted in the action mailed

July 2, 2002 on page 7 that the specification teaches cell lines expressing α_1 subunits can be used to evaluate the effects of pharmaceuticals and/or toxic substance on calcium channels. As the specification also teaches that the calcium channel subunit may be associated with human genetic diseases, the logical conclusion is the agonists and antagonists identified by the claimed screening assays are expected to be useful for treating these diseases. These diseases include including epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome, and Parkinson's disease (*see* specification at page 9). Thus, the specification teaches the claimed processes are useful for identifying agonists and antagonists of T-type calcium channels and diseases associated with such channels.

Second, journal articles published before and at the time the priority application was filed in February of 1997 show that T-type calcium channel agonists were useful for treating a number of diseases set forth in the specification on page 9. These publications are exemplified by the abstracts attached herewith as Exhibits A through H. Abstracts in Exhibits A, B, C, D, E and F show the utility of the T-type calcium channel antagonist mibefradil for treating hypertension, heart disease, and stroke. The abstract in Exhibit G shows the utility of T-type calcium channel blockers nickel and amiloride for affecting the pathogenesis of insulinoma tumor cells. The abstract in Exhibit H shows the utility of the T-type calcium channel blocker zonisamide for treating epileptic seizures. Thus, the utility of T-type calcium channel screening assays for identifying therapeutic molecules was well-established before the priority application was filed.

Third, a compound that binds to one T-type calcium channel binds to all T-type calcium channels. Therefore a compound that treats a disease by binding one T-type channel will bind another T-type calcium channel and exert an effect due to the sequence homology between these channels. As it is well-established there are known T-type calcium channel antagonists useful for treating diseases listed in the specification, the claimed methods have utility for identifying therapeutic molecules. These facts are set forth in the declaration of Dr. Terrence Snutch

executed July 10, 2001 and attached herewith as Exhibit I. The Office must consider the factual analysis by Dr. Snutch as required by the utility examination guidelines (*Official Gazette*, January 30, 2001):

> Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Similarly, Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered.

Because there is no evidence on the record refuting these facts, they must be considered as being true. Thus, the link between the claimed screening assays and the utility of agonists identified by the assays for treating T-type channel-associated diseases is clear.

Fourth, the claimed screening assays have a well-established, specific, substantial and credible utility. The utility is specific because the claimed screening assays are useful for identifying agonists and antagonists of the specified α_1 subunits. The utility is substantial as the agonists and antagonists identified by the screening methods have the real world use of treating diseases specified on page 9 of the specification. The utility is credible because the applicants have generated recombinant cells according to the claimed specification and have screened multiple molecules that act as agonists or antagonists of the α_1 T-subunits (a declaration demonstrating such experiments can be provided to the Office if required). The utility also is credible because the publications submitted in Exhibits A though H demonstrate the usefulness of particular T-type calcium channel agonists for treating diseases. Further, the utility of the claimed screening methods is well-established as evidenced by the state of the art before the filing date of the present patent application. For example, the patch clamp assays and radiolabel ligand assays referenced in the specification on page 22 were well-known in the art as of 1992. *See e.g.,* Williams *et al., Science* 257: 389-395 (1992) and Williams *et al., Neuron*: 71-84 (1992), attached herewith as Exhibits J and K, respectively. Also, the publications in Exhibits A though

H show the utility of T-type calcium channel screening assays for identifying agonists useful from treating certain diseases. Accordingly, the claimed processes have a well-established, specific, substantial and credible utility.

Fifth, the claimed processes require little if no further experimentation for identifying agonists and antagonists useful for treating T-type channel-associated diseases. This feature is highlighted in the Snutch declaration discussed above (Exhibit I) in by journal articles published at the time and before the priority application was filed in 1997 (Exhibits A through H). As the use of the specified α_1 subunits in the claimed screening methods directly identify compounds useful for treating the diseases set forth in the specification, the claimed subject matter is not merely a hunting license as compared to the technology at issue in *Brenner v. Manson*. Also, there is no requirement to determine whether new agonists and antagonists identified by the claimed assays in fact treat a disease *in vivo* in accordance with *In re Brana*, 34 USPQ.2d 1436 (Fed. Cir. 1995). Accordingly, there is little if no further experimentation required to ascertain whether the agonists or antagonists identified by the claimed assays are useful for treating diseases associated with aberrations in α_1 subunits.

Sixth, the Office appears to have ignored the precedence of at least two patents have issued directed to nucleotide sequences encoding T-type calcium channels. These patent are U.S. Patent Nos. 6,358,706 and 6,309,858, attached herewith as Exhibits L and M, respectively. Based on the issuance of these patents the T-type calcium channels clearly are useful as presently claimed. Specifically, they are useful for identifying agonists and antagonists of calcium channel activity which in turn are useful for treating a number of conditions. These utilities are exactly the same as those stated by the patentees in these issued patents. *See e.g.,* columns 6, lines 33-50 in the '706 patent and column 19, lines 53-57 of the '858 patent. In addition, the Office has issued an entire litany of patents with respect to N-type calcium ion channels based on the same logic that applicants have been asserting in the present application. For example, U.S. Patent No. 6,096,514; U.S. Patent No. 6,090,626; U.S. Patent No. 6,013,474; and U.S. Patent

No. 5,876,958 issued with the same requisite utility established for the presently claimed screening assays.

Accordingly, the claimed processes have a well-established, specific, substantial, credible and utilities as taught in the specification. As such, the applicants respectfully request that the Office withdraw the rejections under 35 U.S.C. §§ 101 and 112, first paragraph.

CONCLUSION

Given that the Office switched the species election requirement to a restriction requirement in the previous Office action, the applicants respectfully request that the Office consider the arguments set forth herein which demonstrate that the requirement for restriction is improper. The applicants also respectfully submit that the claimed screening methods have a specific, substantial, credible and well-established utility, and therefore, it is respectfully requested that the Office withdraw the rejections under 35 U.S.C. §§ 101 and 112, first paragraph.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 381092000720.

Respectfully submitted,

Dated: March 26, 2004 By: _____

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